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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,023	07/11/2001	Jack R. Wands	21486-032DIV1	3871

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,023	WANDS ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,39,40,43,45,46,51,52 and 55-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,39,40,45,46,51,52 and 55-59* is/are rejected.

7)☒ Claim(s) *8, and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 5-8, 39, 40, 43, 45, 46, 51, 52, and 55-59 are pending and under consideration.

Claim Rejections - 35 USC § 112, Withdrawn

The rejection of claims 7, 8, 40, 45, 55, 56, and 59 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of the biological deposit statement filed on 04/16/2004.

Claim Rejections - 35 USC § 103, Maintained

Claims 1-3, 5-7, 40, 43, 46, 51, 52, 57, 58, and 59 rejected under 35 U.S.C. 103(a) as being unpatentable over De la Monte et al (IDS 34, 01-1999, Modern Pathology 12:170A) and Lavaissiere et al (IDS C19, 1996, J. Clin. Invest. 98, pages 1313-1323) and further in view of Wer-Remers et al (The American Journal of Gastroentrology, 1997, pages 790-794).

The claims are interpreted as drawn to cancer diagnosis by detecting HAAH in bodily fluid by immunohistochemistry (all the claims except claim 57) and diagnosing pancreatic cancer (claim 57) by detecting HAAH in bodily tissue.

Applicant argues that there is no reason or suggestion to combine Lavaissiere et al., and de la Monte et al., with Wer-Remers et a1., because the type of proteins described and disease indications described by Wer-Remers et al. are significantly different from those described by Lavaissiere et al. or de la Monte et al. None of the references contain any explicit or implicit reasons to combine them. Not all tumor

markers are equal or even equivalent in their structure, function, or distribution. These arguments have been fully considered but found unpersuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Wer-Remers et al teach one skilled in the art tests whether a tumor over-expressed could be detected in bodily fluid, thus providing motivation to one in ordinary skill to look for bodily fluid overexpression of a cancer marker because detecting a cancer biomarker in bodily fluid such as serum would be much less invasive than biopsy of brain, for example. De la Monte et al., and Lavaissiere teach a correlation between overexpression of HAAH polypeptide and cancer. Wer-Remers et al teach one skilled in the art tests whether a tumor over-expressed could be detected in bodily fluid, thus providing motivation to one in ordinary skill to look for bodily fluid overexpression of a cancer marker because detecting a cancer biomarker in bodily fluid such as serum would be much less invasive than biopsy of brain, for example.

Applicant also argues that prior art references must be read as a whole and considered in their entirety. Consideration must be given to where the reference diverges and teaches away from the prior art. In this case, Wer-Remers et al., taken in

its entirety teaches away from the claimed invention. Wer- Remers et al., undertook to evaluate whether tissue expression of CD44 variants and serum levels correlate with one another and whether serum levels of soluble variants have clinical value to evaluate disease. These researchers concluded that serum levels of soluble CD44 or variants thereof did not have diagnostic value. Since the serum concentration is independent of the expression in the primary tumor, the soluble CD44 has little clinical value as a tumor marker. In contrast, Applicants have shown that an increase in HAAH level in bodily fluids is a valuable and reliable diagnostic tool. These arguments have been fully considered but found unpersuasive.

The specification as originally filed does not have data showing a correlation between overexpression of HAAH level in bodily fluids and the various cancers listed in the instant claim 3, and HCC. Thus, "Applicants have shown that an increase in HAAH level in bodily fluids is a valuable and reliable diagnostic tool" argument is not persuasive because applicant argues with a valuable and reliable diagnostic tool not disclosed in the specification. As to Wer-Remers et al., teaching away argument, it is noted that the art has been motivated to see whether a tumor marker detected in tissue is correlated to in serum as shown by Wer-Remer et al. Thus, soluble CD44 marker not being able to use as a cancer diagnostic marker is irrelevant for the instant case. The Office used Wer-Remers et al. reference to show the state of art that one of skill in the art is motivated to use a serum biomarker as diagnostic tool. Applicant is reminded that the instant application does not have any data whether each of the cancers listed in the instant claim 3, and HCC is able to be being diagnosed by detecting an increased level

of HAAH. De la Monte et al., and Lavaissiere et al., teach that overexpression of the protein in tissues from various cancers.

Applicant also argues that the prior art must suggest not only that a certain approach may be tried, but also that there would be a reasonable expectation of success. Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure. Thus, although the Wars- Remers reference may suggest testing a bodily fluid, it in no way suggests an expectation of success in diagnosing malignancies. In fact, it suggests just the opposite - that serum levels are of little or no clinical value. These arguments have been fully considered but found unpersuasive.

De la Monte et al, or Lavaissiere et al teach all the necessary reagents, including FB50 antibody. This antibody appears to be same as the antibody produced by ATCC designation PTA 3386. Note Lavaissiere et al at page 1316, 1st para, line 4. Also note the depost statement filed on 04/16/2004. Wers- Remers reference does not teach the opposite as applicant argues. Rather, Wers- Remers reference teaches serum level of a different marker is not reliable diagnostic tool. The value of the different marker in serum is irrelevant point in this application. What is relevant is that one of skill in the art is motivated to use serum value for diagnostic purpose if can, because obtaining serum value is less invasive than a brain biopsy, for example. De la Monte et al teach HAAH protein overexpression in CNS cancers and De la Monte et al teach overexpression of HAAH in HCC. Teachings of Lavaissiere et al and De la Monte et al suggest that the HAAH overexpression is not limited to a specific tumor or tumor with specific tissue

origin but could be applied to many diverse tumors such as CNS and HCC. Wer-Remers et al teach one skilled in the art tests whether a tumor over-expressed could be detected in bodily fluid, thus providing motivation to one in ordinary skill to look for bodily fluid overexpression of a cancer marker because detecting a cancer biomarker in bodily fluid such as serum would be much less invasive than biopsy of brain, for example.

Since the primary references teach that HAAH could be overexpressed in many tumors and also teach all the necessary reagents for such detection, and secondary reference teach tissue expression and bodily expression is correlated for a certain tumor biomarker in, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to arrive at instant invention with reasonable expectation of success.

As for claim 57, applicant argues that most markers are not useful for detection of a broad range of tumor types, and there is no indication in the cited art that HAAH is useful to generally diagnose any type of malignancy. One of skill in the art would therefore not predict that a tumor marker for HCC and CNS cancer would also be of diagnostic value for pancreatic cancer. Neither Lavaissiere et al. nor de la Monte et al. suggest that HAAH is overexpressed in any other tissue except HCC or CNS cancers, respectively. In view of the absence of any suggestion of specifically diagnosing pancreatic cancer by measuring HAAH, this rejection must be withdrawn. These arguments have been fully considered but found unpersuasive because the HAAH expression is not limited to a specific type of cancers but detected in many different

cancers in the cited prior art. The specification does not disclose any unobvious finding as compared to what has been in the art about HAAH overexpression and cancer.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over De la Monte et al (IDS 34, 01-1999, Modern Pathology 12:170A) and Lavaissiere et al (IDS C19, 1996, J. Clin. Invest. 98, pages 1313-1323) in view of Wer-Remers et al (The American Journal of Gastroentrology, 1997, pages 790-794) as applied to claim 1 above and further in view of Wer-Remers et al (The American Journal of Gastroentrology, 1997, pages 790-794) further in view of Huse (1992, Antibody Engineering, Borrebaeck C ed., page 103-107 only).

The claim is drawn to method of base claim 1 using a single chain antibody.

Applicant argues that as is discussed above, claim 1 is nonobvious over the cited art. Neither de la Monte et al. nor Lavaissiere et al. describe or suggest testing bodily fluid, and the Huse et al. reference also fails to do so. If anything, Wer-Remers et al. indicate that testing the serum for soluble proteins related to a tumor marker that is overexpressed in tissue would be of little or no clinical value. These arguments have been fully considered but found unpersuasive because applicant has not overcome rejection of claim 1 as stated above.

Huse teaches making a single chain antibody from an antibody specific for a known antigen is a routine procedure in the art and one in ordinary skill knows generating a single chain Fv antibody against a useful antigen is cost-effective because it takes less time to purify the antibody. A single chain antibody is another variation of

the primary reference that one in ordinary skill could do with reasonable expectation of success.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

LARRY R. HELMS, PH.D
PRIMARY EXAMINER